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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,115	08/31/2005	Martin Hendrix	01-2112	5580

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EXAMINER	
MURRAY, JEFFREY H	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
12/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,115	HENDRIX ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on February 18, 2005. There are nine claims pending and nine claims under consideration. Claims 6, 11, and 12 have been cancelled. This is the first action on the merits. This invention relates to novel phenyl-substituted pyrazolopyrimidines, process for their preparation, and their use for producing medicaments for improving perception, concentration, learning and/or memory.

Withdrawn Rejections/Objections

2. Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

Specification

3. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Rejections - 35 USC § 112, 1st paragraph

5. Claim 8 and 9 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Method for improving impairments of learning and/or memory is not enabled.

6. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte*

Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* Applicant has provided no guidance, examples, or provided any chemical or biological data and/or testing results of any compounds or medicament that can improving impairments of learning and/or memory whether related to Alzheimer's Disease or not.

There are several different events that can trigger a memory loss or impairment. One such example is post traumatic amnesia. Post-traumatic amnesia is generally due to a head injury (e.g. a fall, a knock on the head). Traumatic amnesia is often transient, but "may be permanent" of either anterograde, retrograde, or mixed type. The extent of the period covered by the amnesia is related to the degree of injury and may give an indication of the prognosis for recovery of other functions. Mild trauma, such as a car accident that results in no more than mild whiplash, might cause the occupant of a car to have no memory of the moments just before the accident due to a brief interruption in the short/long-term memory transfer mechanism. The sufferer may also lose knowledge of who people are, they may remember events, but will not remember faces of them. (http://en.wikipedia.org/wiki/Amnesia).

A stated earlier dementia occurs as a result of the death of brain cells or damage in parts of the brain that deal with our thought processes. This may follow other problems like:

lack of blood/oxygen supply to these brain areas

- head injury e.g. from boxing or whip lash after a car crash
- pressure on the brain e.g. from a tumour
- hydrocephalus (fluid build-up between the brain and the brain lining)
- neurological disease e.g. Parkinson's disease, Creutzfeld Jakob disease (CJD)
- infection e.g. AIDS
- vitamin deficiency
- a long period of excessive alcohol intake

The most common form of dementia is Alzheimer's disease. We do not know what causes Alzheimer's disease but we do know that ageing seems to be a factor. The second most common type of dementia is vascular or multi-infarct dementia. This occurs as a result of lack of blood and oxygen to the brain in a series of tiny 'strokes'.

Unfortunately, most types of dementia cannot be cured. The exceptions are those dementias related to vitamin deficiency (which can be treated with supplements) and head injury (which can be treated through surgery).

(http://www.mentalhealth.org.uk/information/mental-health-a-z/dementia/)

Column 2 of U.S. Patent 7,067,507 reads as follows:

> At present there are no effective treatments for halting, preventing, ***or reversing*** the progression of Alzheimer's Disease. Therefore there is an urgent need for pharmaceutical agents capable of slowing down the progression of Alzheimer's disease and/or preventing it in the first place." (emphasis added)

This statement shows that there is no know way to "improve" Alzheimer's disease.

Amnesia and dementia are just two potential instances where the memory loss can be permanent. In such cases, no matter how little "improvement" is desired within

the human patient, no improvement will ever be seen because improvement is not physically possible.

2) Unpredictability in the art. The invention is directed towards a medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

3) *Number of working examples.* The applicant has provided no working examples of any compounds or medicaments that can improve impairments of learning and/or memory (dementia) whether related to Alzheimer's Disease or not.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Nature of the invention.* The nature of this invention relates to novel phenyl-substituted pyrazolopyrimidines, process for their preparation, and their use for producing medicaments for the treatment of impairments of, or the improvement of perception, concentration, learning and/or memory.

5) State of the Prior Art. These compounds are pyrazolopyrimidines. So far as the examiner is aware, no pyrazolopyrimidines of any kind have been used for the treatment of impairments of, or the improvement of perception, concentration, learning and/or memory.

6) *Level of skill in the art.* The skill level for Alzheimer's Disease is considered low. Alzheimer's Disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research, exceeded in recent years only by research into AIDS and cancer. The channel hypothesis of Alzheimer's disease proposes that the beta-amyloid peptides which accumulate in plaques in the brain actually damage and/or kill neurons by forming ion channels. An abnormal phosphorylation of tau proteins is being investigated as one of the important events in the process leading to their aggregation. There appears to be a specific alteration of a p53-mediated intracellular pathway involved in sensing and repairing DNA damage in peripheral cells, and the role of neuronal apoptosis is under investigation. But even as of 2006, there are great unknowns relating to the links between amyloid-ß and tau, to the mechanisms that determine the selective vulnerability of defined neuronal and glial populations, and to the molecular species that cause nerve cell degeneration. Many kinds of therapies have been investigated in the past, including Hydergine-LC (actually approved by the FDA for Alzheimer's Disease, but later determined to make the disease worse), Cu/Zn chelators (or Cu and Zn homeostasis regulators), endothelin B receptor agonists, α-TNF inhibitors, angiotensin II receptor antagonists, ACE inhibitors, EAA agonists (including partial agoinists), estrogens, metabotropic receptor agonists, muscarinic M2 receptor

antagonists, free-radical scavengers, butyrylcholinesterase inhibitors, cholinergic agonists, potassium-channel blockers, P38 kinase inhibitors, sigma-1 Receptor Agonists, 5-HT1A receptor antagonists, α secretase stimulants, and others. From this immense body of work, only two kinds of drugs ever emerged. Four Acetylcholinesterase inhibitors were found to have some limited value: tacrine (Cognex®, no longer clinically used); donepezil (Aricept®); galantamine (Razadyne®/Reminyl®/Nivalin®) and rivastigmine (Exelon®). In addition, one voltage-dependent NMDA-antagonist, Memantine (Axura®/Akatinol®/Namenda®/Ebixa®) was also found effective. Categories of agents and techniques under investigation as of 2006 include Aß aggregation inhibitors, assorted antioxidants, γ-Secretase modulators, γ-Secretase inhibitors, NGF mimics, PPAR agonists, HMG-CoA reductase inhibitors (statins), Ampakines, Calcium channel blockers, GABA receptor antagonists, Glycogen synthase kinase inhibitors, Intravenous immunoglobulin, Muscarinic receptor agonists, cholinesterase inhibitors, Nicotinic receptor modulators, Passive Aß immunization, Phosphodiesterase inhibitors, Serotonin receptor antagonists, Active Aß immunization, NGF gene therapy, H_3-receptor antagonists, NSAIDs (including NO-NSAIDs and COX-2 Inhibitors), and CB_1 and CB_2 cannabinoid receptor agonists. It is or course entirely possible that one or more of these will eventually be made to work. However, as can be seen by the many, many categories of drugs which never panned out, simply being the subject of active investigation is no indication that enablement is present at that time. The skill level in this art is so low that only Acetylcholinesterase inhibitors and NMDA-antagonists have been made to work.

An additional complication is that there is no good physiological test for Alzheimer's Disease; one must rely on assorted psychological tests. A definitive diagnosis of Alzheimer's Disease can only be done post mortem.

7. Claims 1-5, 7 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound, medicament or the salt thereof, does not reasonably provide enablement for the hydrates and/or hydrates of the salts thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

8. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics* Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* Applicant has provided no guidance, examples, or provided any chemical or biological data and/or testing results of any solvates or solvates of salts in the current application.

2) Unpredictability in the art. Chemistry is unpredictable. See *In Re Marzocchi and Horton* 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) ..... " Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

The scope of "solvates" or "solvates of the salts" are not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Hydrates and solvates cannot be predicted and there fore are not capable of being claimed if the applicant cannot properly enable a particular solvate.

> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. (Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.)

Applicants have argued that the former non-patent literature, Vippagunta, et. al., actually shows enablement for the formation of solvates and hydrates. This argument is not found persuasive.

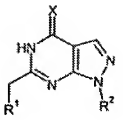
Applicants have cited a section of the article which states that, "...one third of the pharmaceutically active substances are capable of forming crystalline hydrates." Applicants feel that this supports a reasonable expectation of success. Examiner disagrees. First, the statement basically says, 2 out of every 3 pharmaceuticals are NOT capable of forming a hydrate at all. Second, the quoted section of the article states "...capable of forming..." It does not say "will form" or "should be expected to form." The applicants go on to argue another quote which states "crystalline solids ***can*** exist in the forms of polymorphs, hydrates, and solvates..." (emphasis added) which is not to be confused with "do" exist. There is no denying that Vippagunta et. al., shows in limited cases how to make a specific hydrate or solvate. However, the article makes it quite clear that hydrates and solvates are not predictable, not are they easy and routine to form. A hydrate of a compound cannot simply be predicted to form just because a compound is crystalline. If the compound is novel, there is no way to simply determine whether it will form a hydrate (or solvate) or not. There is no test and no chart or diagram to be followed. The formation of hydrates may require much more than just routine experimentation, if it can even be formed at all. Remember, Vippagunta has already taught us that there is a 2 out of 3 chance no hydrate will form regardless of what "pharmaceutically active substance" has been formed.

3) *Number of working examples.* The compound core depicted with specific substituents represent a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any solvates or solvates of acceptable salts mentioned above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Nature of the invention.* The nature of this invention relates to novel phenyl-substituted pyrazolopyrimidines, process for their preparation, and their use for producing medicaments for improving perception, concentration, learning and/or memory.

5) Scope of the Claims. The scope of the claims is all of the thousands of compounds represented by general formula **(I)**:



thus the scope of the claims is very broad.

6) *Level of skill in the art.* The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions.

Double Patenting

9. Applicants have asked that the double patenting rejection from the previous action be held in abeyance. Claims 8-10 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent Publication Application No. 2006/0100222. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 1-3 of U.S. Patent Publication Application No. 2006/0100222 embraces the instant claims 8-10.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. Claims 1-5, 7-9 and 13 are rejected.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is (571) 272-9023. The examiner can normally be reached on Mon-Thurs. 7:30-6pm EST.

13. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached at 571-272-0661. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a US PTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey H Murray/
Patent Examiner
Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624